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ORIGINAL ARTICLE

Correlations between plasma strontium concentration, components of calcium and phosphate metabolism and renal function in type 2 diabetes mellitus

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Abstract

Background: Renal function decline in diabetic kidney disease is accompanied by calcium and phosphate metabolism alterations. Whereas strontium (Sr^{2+}) has many similarities with calcium, little is known about Sr^{2+} in this respect. We studied the association of plasma Sr^{2+} concentration and parameters associated with an altered calcium and phosphate metabolism in diabetic kidney disease.

Materials and methods: Plasma Sr^{2+} concentration was measured in 450 patients included in the DIAbetes and LifEstyle Cohort Twente-1. Patients were classified based on chronic kidney disease (CKD) stages: stages 1-2, stage 3 and stages 4-5 (estimated glomerular filtration rate of $\geq 60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$, $30\text{--}59 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$ and $\leq 29 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$, respectively). The associations between log-transformed plasma Sr^{2+} concentration and parameters of calcium and phosphate metabolism were studied using multivariate linear regression analysis.

Results: Overall, median plasma Sr^{2+} concentration was in normal range, 269 nmol/L, but was progressively higher in patients with lower renal function, that is 246 nmol/L (CKD 1-2), 347 nmol/L (CKD 3) and 419 nmol/L (CKD 4-5). In multivariate analysis, independent associations were found between plasma Sr^{2+} concentration and both eGFR ($\beta = -0.401$, $P < 0.001$) and plasma fibroblast growth factor 23 (FGF23) concentration ($\beta = 0.087$, $P = 0.04$).

Conclusions: We found an independent inverse association between eGFR and plasma Sr^{2+} concentration and an independent association between plasma Sr^{2+} concentration and plasma FGF23 concentration, a marker of deranged calcium and phosphate metabolism. Further research is needed to determine the mechanisms behind these associations and the impact of an elevation in plasma Sr^{2+} concentration on bone mineralization and calcification.

KEYWORDS

calcium- phosphate metabolism, diabetic kidney disease, plasma strontium concentration, type 2 diabetes

1 | INTRODUCTION

The element strontium (Sr^{2+}) is ranked together with calcium, magnesium and barium in the same column of the periodic table of the elements and shares major similarities with calcium. First, both elements become available in the body after absorption in the small intestine and are transported by similar proteins to be stored in bone tissue.¹⁻³ Second, calcium and Sr^{2+} both exit the body through renal excretion as the main route via a similar transport pathway.¹⁻⁴ Finally, Sr^{2+} has a role analogous to calcium—albeit weaker—in several physiological processes, including blood clotting, muscle contraction and bone formation.¹⁻³

Food is the main source of Sr^{2+} , especially leafy vegetables, fruit, seafood, spices and cereals.⁵ Daily intake of Sr^{2+} averages 2 mg, that is considerably lower than 1000-1500 mg calcium intake. An average person contains 47 μg Sr^{2+} and 15 g calcium per kilogram body weight.^{1,4,6} Although literature is scarce, the normal range of plasma Sr^{2+} concentration has been claimed to be 228-354 nmol/L.⁵

Little is known on alterations in circulating plasma Sr^{2+} concentration in patients with renal function impairment.⁷ Chronic kidney disease (CKD) is accompanied by pronounced changes in calcium and phosphate metabolism.^{8,9} Some key features are a tendency towards phosphate retention,¹⁰ resulting in an increased secretion of the phosphaturic peptide hormone fibroblast growth factor 23 (FGF23)^{11,12} and an increase in plasma parathyroid hormone (PTH) concentrations.^{13,14} The latter results in increased bone turnover and therefore stimulates the release of phosphate and calcium from the bones into the circulation.^{6,11} As the plasma calcium concentration is under tight regulation, this increased bone turnover does not result in hypercalcemia.¹⁵

It is unknown whether the changes in calcium and phosphate metabolism associated with progressive CKD also affect plasma Sr^{2+} concentrations. Previously, in animal models with chronic renal failure, signs of increased Sr^{2+} concentrations in serum, bone, the liver and the kidneys have been reported.¹⁶⁻¹⁸ We hypothesize that alterations in mineral metabolism in CKD are associated with increased plasma Sr^{2+} concentrations. Whether this subsequently results in increased renal excretion to prevent increased plasma Sr^{2+} concentrations has not been studied so far.

Therefore, here we investigate the association between plasma Sr^{2+} concentration in diabetic kidney disease and parameters associated with an altered calcium and phosphate metabolism.

2 | MATERIALS AND METHODS

2.1 | Patient inclusion

The study was performed in the DIABetes and LiFEstyle Cohort Twente-1 (DIALECT-1), which was described previously.¹⁹ In short, patients with type 2 diabetes mellitus (T2DM) aged 18 + years were included, and exclusion criteria were renal replacement therapy or inability to understand the informed consent. Patients were included between 2009 and 2016 in the outpatient clinic of internal medicine/nephrology in the ZGT Hospital in Almelo and Hengelo. The study was performed according to the guidelines of good clinical practice and the Declaration of Helsinki. It has been approved by the local institutional review boards (METC registration numbers NL57219.044.16 and 1009.68020) and is registered in the Netherlands Trial Register (NTR trial code 5855). Prior to participation, all participants signed an informed consent form.

2.2 | Data collection

Information on medical condition, medication use and smoking habits were obtained from the electronic patient records and anamnesis. Information concerning alcohol consumption was collected through the questionnaire Food Frequency Questionnaire (FFQ).²⁰ Body dimensions were measured according to standard procedures. Blood pressure was measured in a supine position by an automated device (Dinamap®; GE Medical Systems, Milwaukee, WI, USA) for 15 minutes with 1-minute intervals. The mean systolic and diastolic pressure of the last three measurements was used for further analysis. Blood samples were taken by venipuncture. In addition, every patient collected 24-hour urine. Samples of blood and 24-hours urine were stored for later analysis. Unless noted otherwise, all analyses were performed using routine laboratory procedures. Notably, PTH was analysed using a second-generation immunoassay (Roche Diagnostics, Indianapolis, Indiana, USA) and FGF23 by C-terminal assay (Immutopics, California, USA).

According to standard practice, plasma calcium concentration was corrected for plasma albumin concentration with the formula: corrected plasma calcium concentration (mmol/L) = plasma calcium concentration (mmol/L) + ((40 - plasma albumin concentration (g/L))*0.02).

The renal function was estimated by the CKD Epidemiology Collaboration (CKD-EPI) creatinine-based formula for estimation of the glomerular filtration rate (eGFR).²¹ Albuminuria was defined as urinary albumin excretion ≥ 30 mg/24 h.

2.3 | Sr^{2+} measurements

Plasma Sr^{2+} concentration was determined in stored heparin plasma samples. The samples were diluted 30 times with 0.5% HNO_3 and 0.01% Triton and Rhodium as internal standard (IS) was added. The samples were analysed with inductively coupled plasma mass spectrometry (ICP-MS), NexION 300D (Perkin Elmer, Massachusetts, USA). The same technique was applied to determine urinary Sr^{2+} excretion.

2.4 | Statistical analyses

All statistical analyses were performed using SPSS statistics 24.0. Variables were tested for normality using histograms. Normally distributed variables are presented as the mean and the standard deviation (SD). Skewed variables are presented as the median and interquartile range (IQR, 25th–75th percentile). Binominal variables are displayed as number and proportion.

To evaluate Sr^{2+} levels and components of the calcium and phosphate metabolism in different stages of CKD, the study population was divided into three groups according to CKD stages: CKD stages 1–2 (eGFR $\geq 60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$); CKD stage 3 (eGFR $30\text{--}59 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$); and CKD stages 4–5 (eGFR $\leq 29 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$).²⁰ Differences between the groups were tested using the one-way ANOVA (normal distribution), Kruskal-Wallis (skewed distribution) and chi-square tests. A two-sided P value < 0.05 was considered statistically significant.

To determine the association between components of the calcium and phosphate metabolism and plasma Sr^{2+} concentration, we performed multivariate linear regression analysis. Plasma Sr^{2+} concentration was transformed according to its natural logarithm (LN) to achieve a normal distribution. We performed partial regression analyses to account for collinearity. All possible confounders with a P value < 0.1 in univariate analysis were included in the multivariate linear regression analysis. A backward stepwise elimination with a threshold on $P = 0.05$ was used to select variables in the final model.

3 | RESULTS

3.1 | Study population

A total number of 450 patients, 58% of which were male were included and the mean age was 63 ± 9 years (Table 1), and 58% was male. Mean BMI was $33 \pm 6 \text{ kg/m}^2$ and in the study population 61% of the patients had a BMI above 30 kg/m^2 . Median duration of diabetes was 11

[7–18] years, and the glucose values of the patients were tolerably regulated with a mean HbA_{1c} of $57 \pm 12 \text{ mmol/mol}$. The majority used insulin (64%).

Of the study population, 77% had CKD stages 1–2, 20% had CKD stage 3 and 3% had CKD stages 4–5. Mean age of patients with CKD stages 1–2 was significantly lower (61 ± 9 years) than those with the other CKD stages (68 ± 7 years, $P < 0.001$ and 69 ± 10 years, $P = 0.007$). More patients had albuminuria in CKD stage 3 (47%) and CKD stages 4–5 (64%) than in CKD stages 1–2 (25%), $P < 0.001$. The prevalence of macrovascular disease was higher in CKD stages 4–5 (64%) than in CKD stage 3 (52%) and CKD stages 1–2 (30%), $P < 0.001$.

As expected, the key components of calcium and phosphate metabolism differed between CKD stages: plasma PTH concentration and plasma FGF23 concentration were significantly higher in each subsequent CKD group ($P < 0.001$). Plasma phosphate concentration was highest in CKD stages 4–5, although was not significantly different from the other CKD groups ($P = 0.08$).

Median plasma Sr^{2+} concentration was higher in each subsequent CKD group: 246 [195–317] nmol/L in CKD stages 1–2, 347 [291–412] nmol/L in CKD stage 3 and 419 [348–444] nmol/L in CKD stages 4–5, ($P < 0.001$). Median urinary Sr^{2+} excretion was lower in each subsequent CKD group ($P < 0.001$). There was an inverse correlation between eGFR and LN-transformed plasma Sr^{2+} concentration ($\beta = -0.436$, $P < 0.001$; Figure 1).

3.2 | Relationship between plasma Sr^{2+} concentration and mineral metabolism components

To determine the association between plasma Sr^{2+} concentration and components of calcium and phosphate metabolism, we performed linear regression analysis (Table 2). Because of high collinearity between individual components of the calcium and phosphate axis we performed a partial regression analysis (Table S1). All variables with a $P < 0.10$ in univariate analysis were candidates for the multivariate model. Multivariate linear regression analysis (Table 3) resulted in the following determinants of the plasma Sr^{2+} concentration: gender ($\beta = 0.077$, $P = 0.064$), age ($\beta = -0.082$, $P = 0.090$), eGFR ($\beta = -0.401$, $P < 0.001$), albuminuria ($\beta = 0.091$, $P = 0.034$), plasma PTH concentration ($\beta = 0.144$, $P = 0.002$), in plasma FGF23 concentration ($\beta = 0.087$, $P = 0.035$), 24-hours urinary calcium excretion ($\beta = -0.684$, $P < 0.001$) and in urinary Sr^{2+} excretion ($\beta = 0.670$, $P < 0.001$).

TABLE 1 Characteristics of the study population, in total and based on different CKD stages

Variable	Total population (n = 450)	eGFR \geq 60 CKD stages 1-2 (n = 346)	eGFR 30-59 CKD stage 3 (n = 90)	eGFR \leq 29 CKD stages 4-5 (n = 14)	P value
Age, years	63 \pm 9	61 \pm 9	68 \pm 7 ^b	69 \pm 10 ^a	<0.001
Men, n (%)	262 (58)	203 (59)	50 (56)	8 (57)	0.87
Duration diabetes, years	11 [7-18]	11 [7-18]	12 [6-16]	9 [5-15]	0.62
Plasma HbA _{1c} concentration, mmol/mol	57 \pm 12	58 \pm 12	56 \pm 12	55 \pm 14	0.18
Insulin, n (%)	286 (64)	226 (65)	50 (56)	10 (71)	0.19
Macrovascular disease, n (%)	161 (36)	104 (30)	47 (52)	9 (64)	<0.001
Body mass index, kg/m ²	33 \pm 6	33 \pm 6	33 \pm 6	32 \pm 6	0.75
Systolic blood pressure, mm Hg	139 \pm 16	140 \pm 16	139 \pm 16	137 \pm 15	0.80
Diastolic blood pressure, mm Hg	76 \pm 9	77 \pm 9	74 \pm 10	74 \pm 10	0.07
Smoker, n (%)	75 (17)	57 (17)	16 (18)	2 (14)	0.93
Alcohol, units per month	5 [0-30]	5 [0-32]	4 [0-28]	5 [1-31]	0.76
RAASi, n (%)	298 (66)	216 (62)	71 (79)	11 (79)	0.01
Vitamin D supplements, n (%)	13 (2.8)	3 (0.9)	5 (5.5)	5 (36)	<0.001
Calcium supplements, n (%)	21 (4.7)	18 (5.2)	2 (2.2)	1 (7.1)	0.44
Plasma alkaline phosphatase concentration, U/L	84 \pm 29	82 \pm 28	86 \pm 33	97 \pm 32	0.14
Plasma magnesium concentration, mmol/L	0.77 \pm 0.09	0.77 \pm 0.08	0.77 \pm 0.10	0.79 \pm 0.12	0.59
Plasma phosphate concentration, mmol/L	0.99 \pm 0.18	0.99 \pm 0.18	0.98 \pm 0.18	1.10 \pm 0.34	0.08
Plasma adjusted calcium concentration, mmol/L	2.39 \pm 0.10	2.38 \pm 0.10	2.39 \pm 0.09	2.39 \pm 0.11	0.62
Plasma 25 (OH) vitamin D concentration, nmol/L	42 \pm 20	42 \pm 19	43 \pm 24	46 \pm 24	0.65
Plasma PTH concentration, pmol/L	4.00 [3.01-6.01]	3.60 [2.83-5.04]	6.03 [4.00-9.10]	8.44 [6.98-11.59]	<0.001
Plasma FGF23 concentration, RU/mL	95 [70-142]	84 [66-117]	143 [104-203]	229 [140-662]	<0.001
Plasma Sr ²⁺ concentration, nmol/L	269 [207-355]	246 [195-317]	347 [291-412]	419 [348-444]	<0.001
eGFR, mL·min ⁻¹ ·1.73 m ⁻²	84 [62-97]	90 [77-99]	44 [37-54]	27 [21-28]	<0.001
Albuminuria, n (%)	136 (31)	85 (25)	42 (47)	9 (64)	<0.001
Urinary albumin excretion, mg/24 h	11 [3-66]	9 [2-34]	30 [4-310]	82 [11-677]	<0.001
Urinary phosphate excretion, mmol/24 h	28 \pm 12	29 \pm 12	24 \pm 8 ^b	22 \pm 7	0.001
Urinary calcium excretion, mmol/24 h	3.4 [1.7-6.2]	4.1 [2.4-6.8]	1.4 [0.7-2.3]	0.9 [0.4-1.4]	<0.001
Urinary potassium excretion, mmol/24 h	77 \pm 25	79 \pm 26	70 \pm 21	71 \pm 23 ^a	0.007
Urinary sodium excretion, mmol/24 h	186 \pm 80	195 \pm 81	162 \pm 69 ^b	124 \pm 52 ^a	<0.001
Urinary strontium excretion, nmol/24 h	690 [428-1023]	784 [512-1132]	383 [240-570]	199 [131-371]	<0.001

^asignificant difference with ≤ 90 -60 eGFR mL·min⁻¹·1.73 m⁻².^bsignificant difference with ≤ 90 -60 eGFR mL·min⁻¹·1.73 m⁻².HbA_{1c}, haemoglobin A1c; RAASi, renin-angiotensin-aldosterone system inhibitor.

4 | DISCUSSION

We investigated alterations of the plasma Sr²⁺ concentration in CKD. In the total study population, the median plasma Sr²⁺ concentration was consistent with values reported in the general population,⁴ which illustrates that type 2 diabetes per se is not characterized by increased plasma Sr²⁺ concentration. The main finding in this study was that plasma Sr²⁺ concentration is progressively

increased according to CKD stage and correlates with components of calcium and phosphate metabolism. Plasma Sr²⁺ concentration reached levels considered as above the normal range in CKD stages 4-5.

To the best of our knowledge, the finding that plasma Sr²⁺ concentration is higher when renal function is lower has not been reported previously. The mechanism behind this association is unclear. Possibly, in patients with CKD, there is an increased accumulation of plasma Sr²⁺

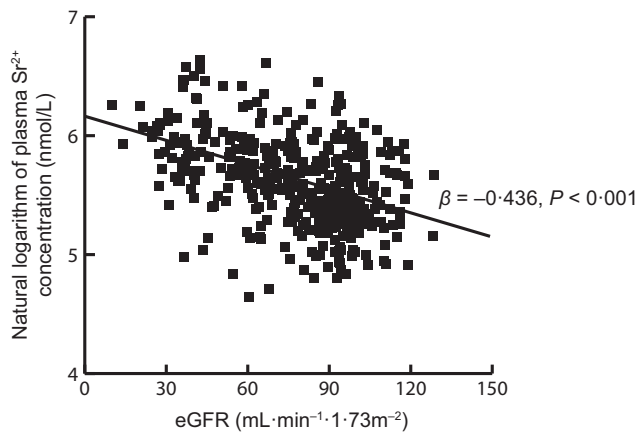


FIGURE 1 Scatterplot of eGFR vs log-transformed plasma Sr^{2+} concentration. There was a statistically significant inverse association between plasma Sr^{2+} concentration and eGFR

concentration by reduced renal excretion of Sr^{2+} . In patients with end-stage renal disease on haemodialysis, increased plasma Sr^{2+} concentration has been interpreted as a phenomenon of accumulation and may be associated with an increased risk for development of osteomalacia.^{16,22-24} From the same point of view, the use of Sr^{2+} supplements has been linked with increased risk of Sr^{2+} accumulation.²²⁻²⁴ The present study shows, however, that increased plasma Sr^{2+} concentration in CKD already occurs in the stages before initiation of dialysis. The hypothesis of Sr^{2+} accumulation in CKD is supported by our finding that urinary excretion of Sr^{2+} is decreased in progressive CKD.

We hypothesized that the negative correlation between plasma Sr^{2+} concentration and eGFR is associated with the alterations in calcium and phosphate metabolism and bone remodelling found in CKD. Therefore, we explored associations between the plasma Sr^{2+} concentration and several variables related to calcium and phosphate metabolism. We found that plasma FGF23 concentration, which is a marker of altered calcium and phosphate metabolism in CKD,¹² was correlated with plasma Sr^{2+} concentration. The associations of both eGFR and FGF23 with plasma Sr^{2+} concentration were independent of other components of calcium and phosphate metabolism. Because plasma calcium concentration is tightly regulated and excess calcium will be periodically excreted in the urine and faeces,¹⁵ increased bone turnover will not result in hypercalcemia. Sr^{2+} and calcium both are transported by similar proteins and are stored in bone tissue.¹⁻³ Given this similarity of calcium and Sr^{2+} , it is likely that increased bone turnover in CKD increases release of both calcium and Sr^{2+} into the circulation. However, we speculate that, unlike plasma calcium concentrations, plasma Sr^{2+} concentration is not tightly regulated and therefore may increase in circumstances of increased bone turnover.^{2,3}

The independent association between plasma FGF23 concentration and plasma Sr^{2+} concentration is intriguing.

TABLE 2 Associations between clinical parameters and plasma Sr^{2+} concentration in patients with type 2 diabetes

Variable	Crude		Adjusted*	
	Stand β	P value	Stand β	P value
Age, years	0.104	0.04		
Men, n (%)	0.101	0.04		
eGFR, $\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$	-0.436	<0.001		
Duration diabetes, years	0.003	0.96	0.032	0.50
Plasma HbA _{1c} concentration, mmol/mol ^a	-0.061	0.22	0.007	0.88
Insulin use, n (%)	0.016	0.75	0.050	0.26
Body mass index, kg/m^2	0.138	0.005	0.086	0.06
Smoker, n (%)	0.043	0.39	0.053	0.23
Alcohol, units per month	0.009	0.86	0.090	0.07
RAASI, n (%) ^b	0.128	0.01	0.026	0.57
Vitamin D supplements, n (%)	0.148	0.003	0.063	0.16
Calcium supplements, n (%)	-0.014	0.78	-0.002	0.96
Plasma alkaline phosphatase concentration, U/L	-0.007	0.88	-0.046	0.31
Plasma magnesium concentration, mmol/L	-0.047	0.35	-0.060	0.18
Plasma phosphate concentration, mmol/L	0.098	0.05	0.076	0.09
Plasma adjusted calcium concentration [†] , mmol/L	0.021	0.68	-0.002	0.97
Plasma 25 (OH) vitamin D concentration, nmol/L	-0.126	0.01	-0.142	0.001
Plasma PTH concentration, pmol/L	0.310	<0.001	0.097	0.06
Ln plasma FGF23 concentration, RU/mL	0.328	<0.001	0.130	0.01
Increased albuminuria, n (%)	0.264	<0.001	0.182	<0.001
Urinary phosphate excretion, mmol/24 h	-0.091	0.07	0.008	0.87
Urinary calcium excretion, mmol/24 h	-0.434	<0.001	-0.275	<0.001
Ln urinary strontium excretion, nmol/24 h	-0.146	0.003	0.155	0.004

^aHbA_{1c} is abbreviation of "Glycated Hemoglobin".

^bRAASI is abbreviation of "Renin Angiotensin Aldosterone System inhibitor".

*Adjusted for age, gender and eGFR.

[†]Plasma calcium concentration was adjusted for plasma albumin concentration. HbA_{1c}, haemoglobin A_{1c}; RAASI, renin-angiotensin-aldosterone system inhibitor; Ln, natural logarithm.

Over the last decade, FGF23 is increasingly recognized as a central component in the altered calcium and phosphate metabolism of CKD¹² and a key component already involved relatively early in the course of the disease.¹¹ The

TABLE 3 Multivariate linear regression model of clinical parameters and plasma Sr^{2+} concentration

Variable	Stand β	P value
Men, n (%)	0.077	0.06
Age, years	-0.082	0.09
eGFR, $\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$	-0.401	<0.001
Albuminuria, n (%)	0.091	0.03
Plasma PTH concentration, pmol/L	0.144	0.002
Ln plasma FGF23 concentration, RU/mL	0.087	0.04
Urinary calcium excretion (mmol/24 h)	-0.684	<0.001
Ln urinary Sr^{2+} excretion, nmol/24 h	0.670	<0.001

$R^2 = 0.441$, $P < 0.001$.

changes in FGF23, PTH, phosphate and calcium as found in the present study are in line with the abundant literature on CKD.^{11,14} Given the cross-sectional nature of our data, a direct link between Sr^{2+} and FGF23 cannot be proven here and would need to be investigated in future studies.

A strength of our study is the fact the study was performed in real-life setting in a large population of patients with T2DM. We used only one geographic area, so that the environmental differences such as the quantity of Sr^{2+} in groundwater and air were minimized.²⁵ A limitation of our study is the cross-sectional design, allowing only research of associations and not of causality.

The question that remains is whether high plasma Sr^{2+} concentration has clinical consequences. Little is known about Sr^{2+} and its function in the human body. In previous trials, low doses of Sr^{2+} supplementation reduced bone resorption and increased bone formation in osteoporotic women.^{16,26} However, in dialysis patients, an accumulation of strontium was associated with a higher risk of osteomalacic lesions.^{16,26} Sr^{2+} plays the same role as calcium in bone formation and blood clotting, albeit to a lesser extent.¹⁻³ It should be kept in mind that plasma Sr^{2+} concentration is 10^6 times lower than plasma calcium concentration.¹ Besides that, no direct toxic effects of Sr^{2+} are currently known.⁵

However, the possibility exists that Sr^{2+} plays a role in the pathophysiology of calcification in blood vessels similar to calcium: Sr^{2+} has already been located in aortic valve plaques.²⁷ Furthermore, the drug Sr^{2+} ranelate has been proven to be effective in patients with untreatable osteoporosis.^{26,28} This demonstrates that Sr^{2+} certainly has some effect on the bone metabolism. Lastly, plasma Sr^{2+} concentration could be a potential marker for bone remodelling.

In conclusion, our study revealed an independent inverse association between eGFR and plasma Sr^{2+} concentration. Furthermore, we found an independent association between plasma Sr^{2+} concentration and plasma FGF23 concentration, a marker of deranged calcium and phosphate

metabolism in CKD. In the total study population, plasma Sr^{2+} concentration was within the normal range.

Further research is needed to determine the mechanism of increased Sr^{2+} when eGFR is low and to investigate the impact of increased Sr^{2+} in bone mineralization and calcification.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

YvdB and CG included patients. AdG, RM, SB, GN and GL contributed resources. SB, GN and GL designed the study. YvdB and CG wrote the manuscript. AdG, RM, SB, GN and GL reviewed the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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